AMENDMENTS TO THE SPECIFICATION

In the Specification

1.) Please insert the following paragraph on page 1, immediately following the title of the application, as follows:

PRIORITY CLAIM

This is the § 371 U.S. National Stage of International Application No. PCT/US2004/037600, filed on November 10, 2004, which in turn claims the benefit of U.S. Provisional Application No. 60/527,882, filed on December 4, 2003, which is incorporated herein by reference in its entirety.

2.) Please amend the **Summary of the Invention**, beginning on page 3, line 1 of the specification as follows:

The present invention is also directed to an antibody or an antigen-binding fragment thereof, wherein said antibody comprises a variable heavy chain amino acid sequence of SEQ ID NO. ~~50~~45 and a variable light chain amino acid sequence of SEQ ID NO. ~~48~~46, designated herein as HuAIP12.

The present invention is also directed to a method of reducing severity of at least one symptom of inflammatory bowel disease in a subject in need thereof comprising administering to said subject an effective amount of an antibody or an antigen-binding fragment thereof comprising a variable heavy chain amino acid sequence of SEQ ID NO. ~~50~~45 and a variable light chain amino acid sequence of SEQ ID NO. ~~48~~46.

The present invention is also directed to a pharmaceutical composition comprising an antibody or an antigen-binding fragment thereof comprising a variable heavy chain amino acid sequence of SEQ ID NO. ~~50~~45 and a variable light chain amino acid sequence of SEQ ID NO. ~~48~~46.

The present invention is also directed to an antibody or an antigen-binding fragment thereof, wherein said antibody comprises a variable heavy chain amino acid sequence of SEQ ID NO:78 and a variable light chain amino acid sequence of SEQ ID NO. ~~48~~46, designated herein as the HuAIP12 T55~~4~~I variant.

The present invention is also directed to a method of reducing severity of at least one symptom of inflammatory bowel disease in a subject in need thereof comprising administering to said subject an effective amount of an antibody or an antigen-binding fragment thereof comprising a variable heavy chain amino acid sequence of SEQ ID NO. 78 and a variable light chain amino acid sequence of SEQ ID NO. ~~48~~46.

The present invention is also directed to a pharmaceutical composition comprising an antibody or an antigen-binding fragment thereof comprising a variable heavy chain amino acid sequence of SEQ ID NO. 78 and a variable light chain amino acid sequence of SEQ ID NO. ~~48~~46.

3.) Please amend the **Brief Description of the Drawings**, beginning on page 3, line 30 of the specification as follows:

Figure 1A depicts the HuAIP12 VH amino acid sequence (SEQ ID NO. ~~50~~45), the HuAIP13 VH amino acid sequence (SEQ ID NO. ~~18~~13), the HuAIP12 T55I variant VH amino acid sequence (SEQ ID NO. 78) and the HuAIP12 G104A variant VH amino acid sequence (SEQ ID NO. 79).

Figure 1B depicts the HuAIP12 VL amino acid sequence (SEQ ID NO. ~~48~~46) and the HuAIP13 VL amino acid sequence (SEQ ID NO. ~~17~~15).

Figure 2 depicts the inhibition of IP-10 mediated chemotaxis of BA/F3-CXCR3 cells by the HuAIP12 T55~~4~~I variant antibody as compared to the original, unmodified HuAIP12 antibody.

4.) Please amend the paragraph beginning on page 9, line 3 of the specification as follows:

The amino acid sequence of the full-length wild-type human IP-10 is presented in SEQ ID NO: 1 (MNQTAILICC LIFLTLSGIQ GVPLSRTVRC TCISISNQPV NPRSLEKLEI IPASQFCPRV EIIATMKKKG EKRCLNPESK AIKNLLKAVS KERSKRSP). A "functionally active" IP-10 fragment or derivative exhibits one or more functional activities associated with the full-length, wild-type IP-10 protein, such as antigenic or immunogenic activity, ability to bind natural cellular substrates, such as its cognate receptor, etc. The functional activity of IP-10 proteins, derivatives and fragments can be assayed by various methods known to one skilled in the art (Coligan et al., eds., Current Protocols in Protein Science, John Wiley & Sons, Inc., Somerset, New Jersey (1998)). For purposes herein, functionally active fragments also include those fragments that comprise one or more structural domains of an IP-10 polypeptide, such as a binding domain. Protein domains can be identified using the PFAM program (Bateman A., et al., Nucleic Acids Res. 27: 260-2 (1999)~~; http://pfam.wustl.edu~~).

5.) Please amend the paragraph beginning on page 10, line 27 of the specification as follows:

The amino acid sequences of the mature heavy chain variable region and the mature light chain variable region of AIP13 are depicted in SEQ ID NOs: 3 and 4, respectively. The amino acid sequences of the mature heavy chain variable region and the mature light chain variable region of HuAIP13 are depicted in SEQ ID NOs: 13 and ~~14~~15, respectively. SEQ ID NOs: 5, 6, and 7 depict the AIP13 and HuAIP13 amino acid sequences of the heavy chain CDR1 (DYSMH), CDR2 (WINTEIGEPTYADDFKG), and CDR3 (NYDYDAYFDV), respectively. SEQ ID NOs: 8, 9, and 10 depict the AIP13 and HuAIP13 amino acid sequences of the light chain CDR1 (KADQDINKYIA), CDR2 (HTSTLQP), and CDR3 (LQYDSLLFT), respectively.

6.) Please amend the paragraph beginning on page 11, line 12 of the specification as follows:

The present invention includes the analogs of the antibodies or antibody fragments described herein. These analogs should retain the antigen-binding utility. Preferred analogs include a) the CDRs comprising an amino acid sequences sharing at least 60%, 80% or 90-95% amino acid sequence identity with SEQ ID NOs: 5, 6, 7, 8, 9, or 10; b) the CDRs comprising an amino acid sequences sharing at least 60%, 80% or 90-95% amino acid sequence identity with SEQ ID NOs: 5, 73, 74, 75, 76, or 77; c) a mature heavy chain variable region comprising an amino acid sequences sharing at least 60%, 80% or 90-95% amino acid sequence identity with SEQ ID NO: 3 or 13; and/or a mature light chain variable region comprising an amino acid sequences sharing at least 60%, 80% or 90-95% amino acid sequence identity with SEQ ID NO: 4 or ~~14~~15; d) a mature heavy chain variable region comprising an amino acid sequences sharing at least 60%, 80% or 90-95% amino acid sequence identity with SEQ ID NO: 41 or 45; and/or a mature light chain variable region comprising an amino acid sequences sharing at least 60%, 80% or 90-95% amino acid sequence identity with SEQ ID NO: 42 or 46; and e) antibodies or antibody fragments comprising these heavy chain and/or light chain variable regions. More preferred analogs of exemplified antibodies differ from exemplified antibodies or antibody fragments by conservative amino acid substitutions. For the purpose of classifying amino acids substitutions as conservative or nonconservative, amino acids may be grouped as follows: Group I (hydrophobic sidechains): met, ala, val, leu, ile; Group II (neutral hydrophilic side chains): cys, ser, thr; Group III (acidic side chains): asp, glu; Group IV (basic side chains): asn, gln, his, lys, arg; Group V (residues influencing chain orientation): gly, pro; and Group VI (aromatic side chains): trp, tyr, phe. Conservative substitutions involve substitutions between amino acids in the same class. Non-conservative substitutions constitute exchanging a member of one of these classes for a member of another. The analogs of the present invention can be made by amino acid substitutions via mutagenesis methods known in the art.

7.) Please amend the paragraph beginning on page 15, line 25 of the specification as follows:

Anti-IP-10 fully human antibodies are also included in the present invention. In a preferred embodiment of the present invention, said fully human antibodies are isolated human antibodies and neutralize the activities of IP-10 described herein. ~~HuAIF13~~HuAIP13 is an exemplification of humanized antibody that binds to IP-10. The amino acid sequences of the ~~HuAIF13~~HuAIP13 heavy chain variable region and light chain variable region are SEQ ID No.:13 and ~~14~~15, respectively. ~~HuAIF12~~HuAIP12 is another exemplification of humanized antibody that binds to IP-10. The amino acid sequences of the ~~HuAIF13~~HuAIP12 heavy chain variable region and light chain variable region are SEQ ID No.:45 and 46, respectively.

8.) Please amend the paragraph beginning on page 27, line 13 of the specification as follows:

A panel of mouse anti-human-IP-10 monoclonal antibodies that bind to recombinant hIP-10 was generated. These antibodies also bind to supernatants from the PHA blasts. Several of the monoclonal antibodies against hIP-10 effectively neutralized the chemotaxis of PHA and LPS blasts in a dose-dependent manner. All of these monoclonal antibodies also bind to the mammalian-cell-expressed cynomolgus IP-10 ~~(Table 1)~~.

9.) Please amend the paragraph beginning on page 34, line 1 of the specification as follows:

The resulting V gene fragments were cloned into the mammalian expression vectors pHuCkappa.rgpt.dE and pVg1.D.Tt (described, *supra*), and then combined to generate a single expression vector for co-expression of the light and heavy chains. The DNA sequences of the humanized VL and VH mini-exons are depicted in SEQ ID Nos: 17 and 19, respectively, and deduced amino acid sequences ~~)~~ of the humanized VL and VH mini-exons ~~aredepicted~~ are depicted in SEQ ID Nos: 18 and 20, respectively.

10.) Please amend the paragraph beginning on page 44, line 28 of the specification as follows:

HuAIP12 and HuAIP13 are humanized IgG1/κ forms of the murine monoclonal antibodies AIP12 and AIP13, respectively, which bind to and neutralize human IP-10 (Examples 5 and 6). The VL and VH amino acid sequences of HuAIP12 are shown in SEQ ID NOS. ~~48~~46 and ~~50~~45, respectively. The VL and VH amino acid sequences of HuAIP13 are shown in SEQ ID NOS. ~~17~~15 and ~~18~~,13, respectively. Biacore™ analysis indicated that the binding affinity of HuAIP12 to human IP-10 is approximately 2.6 fold higher than that of HuAIP13 (Table 3).